

Malaria and Pregnancy: A Global Health Perspective

Julianna Schantz-Dunn, MD,* Nawal M. Nour, MD, MPH[†]

*Brigham and Women's Hospital, Division of Global Obstetrics and Gynecology, Harvard Medical School, Boston, MA; [†]Department of Maternal-Fetal Medicine, Brigham and Women's Hospital, Division of Global Obstetrics and Gynecology, Harvard Medical School, Boston, MA

Malaria, a parasitic infection transmitted by mosquitoes, is one of the most devastating infectious diseases, killing more than 1 million people annually. Pregnant women, children, and immunocompromised individuals have the highest morbidity and mortality, and Africa bears the heaviest burden. The World Health Organization defines malaria as a disease of poverty caused by poverty. Pregnant women infected with malaria usually have more severe symptoms and outcomes, with higher rates of miscarriage, intrauterine demise, premature delivery, low-birth-weight neonates, and neonatal death. They are also at a higher risk for severe anemia and maternal death. Malaria can be prevented with appropriate drugs, bed nets treated with insecticide, and effective educational outreach programs.

[Rev Obstet Gynecol. 2009;2(3):186-192 doi: 10.3909/riog0091]

© 2009 MedReviews®, LLC

Key words: *Plasmodium falciparum* • Malaria, pregnancy • Malaria, immunocompromised host • Malaria, neonates

Malaria is the second most common cause of infectious disease-related death in the world, after tuberculosis. It is estimated to affect between 350 to 500 million people annually and accounts for 1 to 3 million deaths per year.^{1,2} Sub-Saharan Africa has the largest burden of malarial disease, with over 90% of the world's malaria-related deaths occurring in this region. Twenty-five million pregnant women are currently at risk for malaria, and, according to the World Health Organization (WHO), malaria accounts for over 10,000 maternal and 200,000 neonatal deaths per year.³

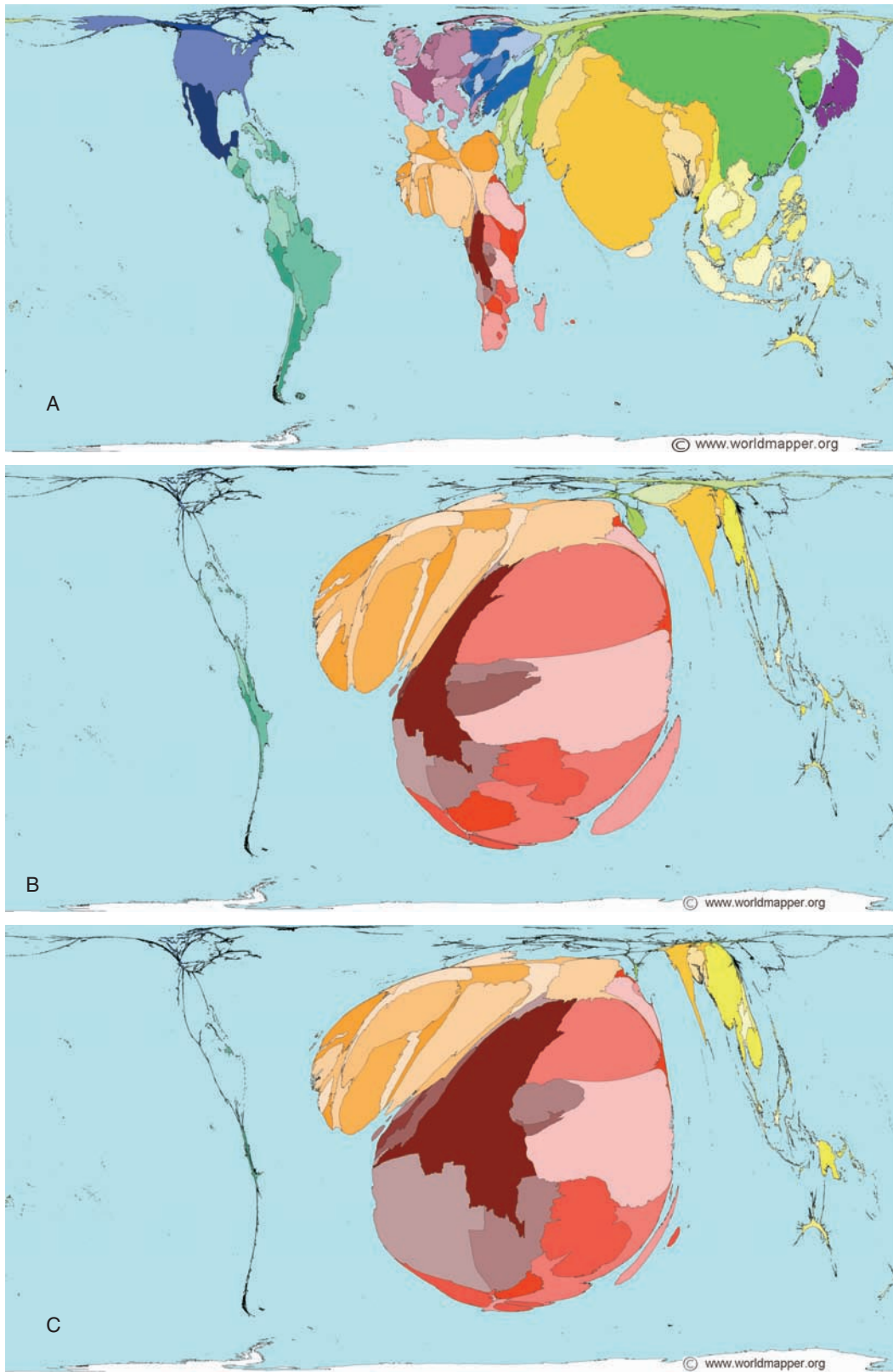


Figure 1. (A) World territories. The size of each territory shows the relative proportion of the world's population. (B) Worldwide distribution of malaria cases. The size of each territory shows the proportion of all people living with malaria. (C) Worldwide distribution of malaria deaths. The size of each territory shows the proportion of worldwide deaths from malaria that occur there. © 2006 SASI Group (University of Sheffield) and Mark Newman (University of Michigan). Reproduced with permission.

These figures may underestimate the impact malaria has in maternal morbidity and mortality. A recent study from Mozambique that assigned cause of maternal death via autopsy examination found that up to 10% of maternal deaths were directly attributed to malarial infection and 13% were secondary to human immunodeficiency virus (HIV)/AIDS, which can be exacerbated by coexisting malarial infection.⁴ This suggests that in parts

Europe and parts of Central and South America, have also had success in eradicating malaria, whereas Sub-Saharan Africa continues to bear the burden of disease, as illustrated in Figure 1.

Pathophysiology

Malaria is transmitted when an infected mosquito takes a human blood meal and the *Plasmodium* sporozoites are transferred from the saliva of the

the body's inflammatory response.⁷ Malarial infection causes marked immunoglobulin synthesis and, in the case of *P falciparum*, creates immunoglobulin complexes and increased production of tumor necrosis factor. The ability of *P falciparum* to cause cytoadherence of erythrocytes to vascular walls leads to sequestration of infected cells in small blood vessels, causing end organ damage via hemorrhage or infarct.^{6,7} Phagocytosis of infected blood cells in the spleen helps clear infection, but also contributes to profound anemia and folic acid deficiency.

It has been established that repeated malarial infections lead to some immunity. In fact, in areas where malaria incidence is episodic rather than endemic, patients will present with more severe forms of the disease, as their previously "learned immunity" appears to fade over time. It is not surprising, therefore, that malaria-naïve and immunocompromised patients are prone to more severe infection. This puts pregnant women, children, travelers to endemic regions, and persons with coexisting

In parts of the world where malaria is endemic, it may directly contribute to almost 25% of all maternal deaths.

of the world where malaria is endemic, it may directly contribute to almost 25% of all maternal deaths.

Malaria in pregnancy also contributes to significant perinatal morbidity and mortality. Infection is known to cause higher rates of miscarriage, intrauterine demise, premature delivery, low-birth-weight neonates, and neonatal death. As funding increases to combat both malaria and maternal mortality, understanding how malaria specifically affects pregnant women is crucial in our efforts to improve maternal and perinatal health and curb the spread of this preventable infectious disease.

Epidemiology

Malaria is a parasitic infection caused by the 4 species of *Plasmodium* that infect humans: *vivax*, *ovale*, *malariae*, and *falciparum*. Of these, *Plasmodium falciparum* is the most deadly. The infection is transmitted by the female anopheline mosquito; therefore factors that influence mosquito breeding, such as temperature, humidity, and rainfall, affect malaria incidence.² In the United States, malaria was eradicated in the 1940s after widespread spraying of dichlorodiphenyl-trichloroethane (DDT) in the South.⁵ Other areas of the world, including

mosquito into the capillary bed of the host. Within hours, the parasite will migrate to the liver, where it undergoes further cycling and replication before being released back into the host's bloodstream (Figure 2).⁶

The incubation period, from the time of mosquito bite until clinical symptoms appear, is typically 7 to 30 days. Symptoms include fever, headache, nausea, vomiting, and myalgias. Due to the cycling parasitemia in the bloodstream, patients

Pregnant women, children, travelers to endemic regions, and persons with coexisting HIV infection are at highest risk for morbidity and mortality secondary to malarial infection.

will often experience symptoms every 2 to 3 days, depending on the type of *Plasmodium* with which they are infected.

In the human, plasmodial infection is a complicated reproductive life cycle involving hepatic and erythrocytic infection. Once the sporozoite enters the liver, it multiplies and exits into the bloodstream in the merozoite form. The merozoite then invades erythrocytes, leading to phagocytosis of infected blood cells by the spleen. Malarial symptoms are caused mainly by the red blood cell invasion and

HIV infection at highest risk for morbidity and mortality secondary to malarial infection.

Diagnosis

Clinically, malaria is categorized into 2 types: uncomplicated and severe. Uncomplicated malaria is characterized by a *cold stage*, consisting of cold sensation and shivering, and a *hot stage*, with fever, headache, sweating, and occasionally seizures. Symptoms generally last for 6 to 10 hours and occur every 2 to 3 days, depending on the infecting species. Severe malaria,

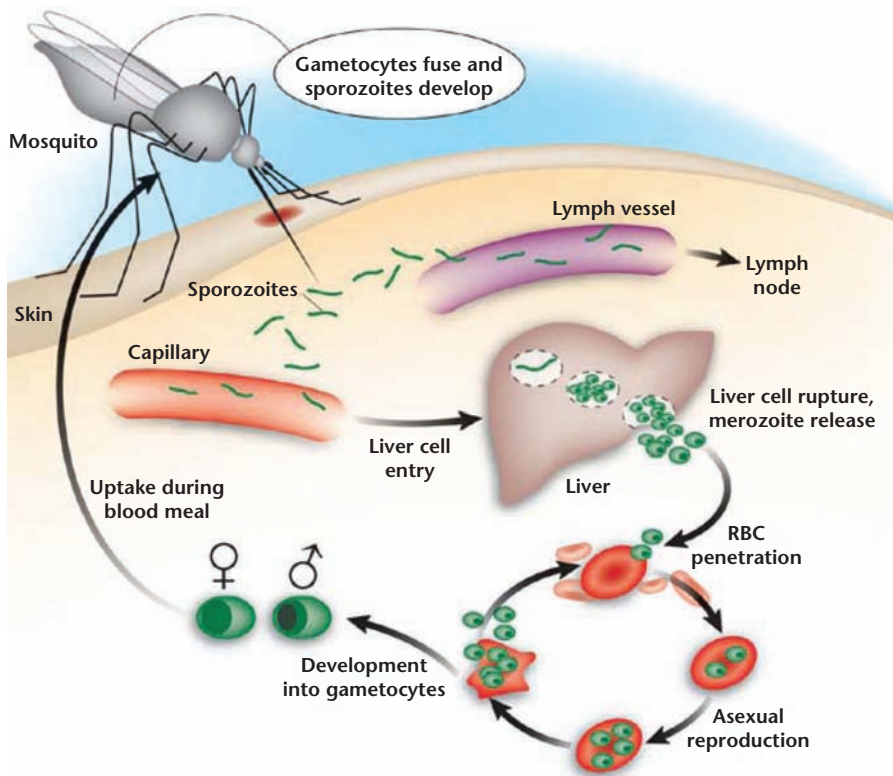


Figure 2. Life cycle of malaria infection. Reproduced with permission from Jones MK, Good MF. Malaria parasites up close. Nat Med. 2006;12:170-171.

the second subtype, is generally caused by *P. falciparum* infection and is characterized clinically by organ damage or blood abnormalities, including cerebral malaria, hemolysis and severe anemia, pulmonary edema, acute respiratory distress syndrome, thrombocytopenia, renal failure, and cardiovascular collapse. Microscopically, it is characterized by a parasitemia level of greater than 5%. Severe anemia is a medical emergency.^{1,7}

Historically, diagnosis of malaria has relied on clinical history or microscopic identification of the asexual stages of the parasite on a blood smear fixed with Giemsa stain. More recent advances in diagnosis have been made with the introduction of rapid diagnostic tests (RDTs), immunochromatographic dipstick assays that act in a similar fashion to a

home pregnancy test. Most of the RDTs report sensitivities above 90% for detection of malaria, with increasing sensitivity as the level of parasitemia increases. It is hypothesized that malarial antigen detection via RDTs may be a better diagnostic tool for use in pregnant women, as much of *P. falciparum* sequesters in the placenta and therefore may not be visible on a standard smear, producing false-negative results if diagnosis is based on microscopy and clinical symptoms alone.⁸

Malaria in Pregnancy

Pregnant women are 3 times more likely to suffer from severe disease as a result of malarial infection compared with their nonpregnant counterparts, and have a mortality rate from severe disease that approaches 50%.^{6,9} In areas endemic for malaria,

it is estimated that at least 25% of pregnant women are infected with malaria, with the highest risk for infection and morbidity in primigravidas, adolescents, and those coinfecting with HIV.¹⁰ The second trimester appears to bring the highest rate of infection, supporting the need for antepartum care as part of malarial prevention and treatment efforts.

It is hypothesized that the majority of sequelae in pregnancy results from 2 main factors: the immunocompromised state of pregnancy and placental sequestration of infected erythrocytes.

As discussed previously, adults who live in malaria-endemic regions generally have some acquired immunity to malaria infection as a result of immunoglobulin production during prior infections in childhood. This immunity diminishes significantly in pregnancy, particularly in primigravidas. A recent study of 300 women delivering in rural Ghana showed higher rates of anemia, clinical malaria, and placental burden of infection among primigravidas compared with multigravidas. The study also noted that babies born to mothers with placental malaria infection were more than twice as likely to be underweight at birth.¹¹

Splenic sequestration of malaria-infected erythrocytes leads to folic acid deficiency and microcytic anemia in adults. In pregnant women, additional sequestration of malaria-infected erythrocytes occurs in the placenta. Pregnant women therefore suffer disproportionately from severe anemia as a result of infection. In Africa, it has been estimated that malaria is responsible for 25% of severe anemia during pregnancy (defined as hemoglobin less than 7 gm/dL).¹⁰ Women with severe anemia are at higher risk for morbidities such as congestive heart failure, fetal demise, and mortality associated with



Figure 3. Severe anemia in the third trimester of pregnancy (hemocrit, 13%). Photo courtesy of J. Schantz-Dunn (Belladere, Haiti, 2008).

hemorrhage at the time of delivery (Figure 3).

Interestingly, the greatest degree of placental infestation is seen in women who have the highest level of immunity, leading to milder maternal symptoms and a disproportionate increase in fetal complications.⁶ It could

and hypoglycemia during infection. This contributes to the severity of disease during pregnancy. Other maternal effects of malarial infection result from the “stickiness” of the infected erythrocytes that become trapped in small vessels, resulting in cerebral malaria, renal failure, and thrombo-

Fetal complications result from placental inflammation and manifest as stillbirth, intrauterine growth restriction, and low-birth-weight neonates.

be hypothesized, therefore, that although primigravidas may develop the clinical symptoms of malaria, women with higher immunity may not demonstrate symptoms, will not receive treatment, and will build a higher placental parasite burden. Fetal complications result from this placental inflammation, as well as maternal anemia, and manifest as stillbirth, intrauterine growth restriction, and low-birth-weight neonates. Low-birth-weight neonates, in turn, are at higher risk for neonatal and newborn death. Congenital malaria is a relatively rare complication in areas with endemic malaria; however, newborn parasitemia may present 2 to 3 months after delivery when maternal antibodies wear off.

It is also thought that infected erythrocytes collected in the placenta stimulate pancreatic β -cell production of insulin, leading to hyperinsulinemia

cytopenia. Case reports confusing malaria infection with HELLP syndrome demonstrate the overlap in clinical and laboratory findings between the 2 diseases and the importance of proper diagnosis.¹²

Malaria and HIV

Each year, approximately 50 million women become pregnant in malaria-endemic regions. Among these women, 1 million are estimated to be

HIV infection increases the pregnant woman's susceptibility to malaria and the morbidity associated with malaria, resulting in higher incidences of severe anemia and low-birth-weight neonates in coinfecting women.¹³ Malarial infection in HIV-positive women is associated with higher levels of parasitemia, leading to a greater risk of severe anemia. Likewise, HIV viral load is increased, creating opportunity for infection and more severe disease.¹⁴

Prevention

Current prevention of malarial disease in pregnancy relies on 2 main strategies: providing pregnant women with insecticide-treated bed nets (ITN) and intermittent presumptive treatment (IPT) with antimalarial medications. IPT refers to the administration of 2 or more doses of chemoprophylaxis after 20 weeks of gestation in an attempt to reduce subclinical malarial load.

In a Cochrane Review comparing malarial chemoprophylaxis with no prophylaxis during pregnancy, Garner and Gülmezoglu found a significant reduction in maternal anemia, parasitemia, and perinatal death, and a higher mean birth weight in the groups given IPT.¹⁵ More recent studies in Nigeria that examined specific IPT regimens found significant reductions in maternal anemia with the use of sulfadoxine-pyrimethamine as compared with chloroquine,

As a result of the impaired immune state, HIV infection increases the pregnant woman's susceptibility to malaria and the morbidity associated with malaria, resulting in higher incidences of severe anemia and low-birth-weight neonates in coinfecting women.

infected with both malaria and HIV, both of which are preventable, treatable, and responsible for significant maternal and neonatal morbidity.³ As a result of the impaired immune state,

pyrimethamine, or no prophylaxis.^{16,17} Sulfadoxine-pyrimethamine has been found safe in pregnancy when used intermittently as part of IPT.¹⁸

Although the WHO currently recommends that all pregnant women living in malaria-endemic regions use insecticide-treated bed nets and IPTp-SP (intermittent presumptive treatment in pregnancy with at least 2 doses of sulfadoxine-pyrimethamine), studies show poor uptake of both preventative efforts among pregnant women. A recent survey among postpartum women in rural Uganda, in which 88% had made more than 1 prenatal visit, found that only 31% of women used a bed net during pregnancy and only 36% had received 2 doses of IPTp-SP.¹⁹ This indicates that as access to and utilization of antepartum care increase, there is still a role for improved administration of IPTp-SP and education regarding bed net use.

Additional constraints appear when there is concurrent use of IPT with antiretroviral medications for the treatment of HIV and prevention of vertical transmission secondary to limited knowledge surrounding the drug-drug interactions. In particular, review of the literature suggests increased risk of cutaneous and hepatic toxicity when IPT is used in conjunction with nevirapine, and increased risk of bone marrow suppression when used in conjunction with zidovudine, leading to unintended

morbidity associated with treatment of the 2 diseases.¹³

Treatment

Treatment of uncomplicated malaria in pregnancy is a balance between potential fetal adverse effects from drug toxicity and improved clinical status with clearance of the parasite. In 2006, the WHO recommended a combination of quinine and clindamycin for treatment of uncomplicated malaria in pregnancy; however, there is a risk of hypoglycemia with quinine use, as well as increasingly drug-resistant *P falciparum*. More data currently support the use of artemisinin-based combination therapy, which appears safe and effective in pregnancy.²⁰

For severe malaria in pregnancy, the WHO currently recommends treatment with either intravenous (IV) quinine or artesunate, or IV artesunate in the second and third trimesters. Not only should IV quinine be avoided in the second and third trimesters as it is associated with recurrent hypoglycemia, but evidence supports the superiority of artesunate over quinine in the nonpregnant patient. In epidemic situations, if IV or intramuscular medication is unavailable, patients should receive artesunate supposito-

ries and be transferred to a higher-level facility.⁹

Conclusion

Malaria has become one of the most challenging infectious diseases to eradicate in Africa. The overall disease burden is devastating youth, women, and health systems. Malaria accounts for 40% of public health expenditure, 30% to 50% of inpatient admission, and up to 50% of outpatient visits in endemic regions. It has affected Africa's human resources and directly lowered its annual economic growth. It not only debilitates the workforce, but keeps children from going to school, prevents pregnant mothers from effectively caring for their families, and decreases the likelihood of a healthy pregnancy outcome. Governments and donors have recognized this extraordinary toll and have increased their commitment toward prevention, treatment, and eradication. More successful programs have included reducing tariffs on ITNs to make them more affordable, incorporating infectious disease in reproductive health programs, and intermittent preventive treatment. With sustained governmental commitment and financial resources, the eradication of malaria can succeed. ■

Main Points

- The United States, Europe, and parts of Central and South America have had success in eradicating malaria, whereas sub-Saharan Africa continues to bear the burden of disease.
- Recent advances in diagnosis include immunochromatographic dipstick assays that report sensitivity above 90% and may be a better diagnostic tool for use in pregnant women.
- Pregnant women are 3 times more likely to suffer from severe disease as compared with their nonpregnant counterparts and have a mortality rate from severe malarial infection that approaches 50%.
- Pregnant women suffer disproportionately from severe anemia as a result of malarial infection. Women with severe anemia are at higher risk for congestive heart failure, fetal demise, and mortality associated with hemorrhage at the time of delivery.
- Current prevention of malarial disease in pregnancy relies on providing women with insecticide-treated bed nets and intermittent presumptive treatment.

References

1. Malaria facts. Centers for Disease Control and Prevention Web site. <http://www.cdc.gov/malaria/facts.htm>. Updated April 11, 2007. Accessed August 1, 2009.
2. Malaria. The Global Fund Web site. http://www.theglobalfund.org/documents/publications/diseasereport/disease_report_malaria_en.pdf Accessed August 1, 2009.
3. Global Malaria Programme: pregnant women and infants. World Health Organization Web site. <http://apps.who.int/malaria/pregnantwomenandinfants.html>. Accessed July 30, 2009.
4. Menéndez C, Romagosa C, Ismail MR, et al. An autopsy study of maternal mortality in Mozambique: the contribution of infectious diseases. *PLoS Med*. 2008;5:e44.
5. Williams LL Jr. Malaria eradication in the United States. *Am J Public Health Nations Health*. 1963; 53:17-21.
6. Monif GRG, Baker DA, eds. *Infectious Disease in Obstetrics and Gynecology*. 6th ed. New York: Parthenon; 2004:280-286.
7. White NJ, Breman JG. Malaria. In: Fauci AS, Braunwald E, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine*. 17th ed. New York: McGraw-Hill; 2008:1280-1293.
8. Murray CK, Bennet JW. Rapid diagnosis of malaria. *Interdiscip Perspect Infect Dis*. 2009; 2009:415953.
9. World Health Organization. *Guidelines for the Treatment of Malaria*. Geneva: World Health Organization; 2006:58.
10. Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis*. 2007;7:93-104.
11. Ofori MF, Ansah E, Agyepong I, et al. Pregnancy-associated malaria in a rural community of Ghana. *Ghana Med J*. 2009;43:13-18.
12. Ducarme G, Thuillier C, Wernet A, et al. Malaria in pregnant woman masquerading as HELLP syndrome. *Am J Perinatal*. doi: 10.1055/s-0029-1234035.
13. Brentlinger PE, Behrens CB, Micek MA. Challenges in the concurrent management of malaria and HIV in pregnancy in sub-Saharan Africa. *Lancet Infect Dis*. 2006;6: 100-111.
14. Briand V, Badaut C, Cot M. Placental malaria, maternal HIV infection and infant morbidity. *Ann Trop Paediatr*. 2009;29:71-83.
15. Garner P, Gülmezoglu AM. Drugs for preventing malaria in pregnant women. *Cochrane Database Syst Rev*. 2006;(4):CD000169.
16. Asa OO, Onayade AA, Fatusi AO, et al. Efficacy of intermittent preventive treatment of malaria with sulphadoxine-pyrimethamine in preventing anaemia in pregnancy among Nigerian women. *Matern Child Health J*. 2008;12:692-698.
17. Falade CO, Yusuf BO, Fadero FF, et al. Intermittent preventive treatment with sulphadoxine-pyrimethamine is effective in preventing maternal and placental malaria in Ibadan, southwestern Nigeria. *Malar J*. 2007;6:88.
18. Peters PJ, Thigpen MC, Parise ME, Newman RD. Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Saf*. 2007;30:481-501.
19. Kiwuwa Ms, Mufubenga P. Use of antenatal care, maternity services, intermittent presumptive treatment and insecticide treated bed nets by pregnant women in Luwero district, Uganda. *Malar J*. 2008;7:44.
20. Orton LC, Omari AA. Drugs for treating uncomplicated malaria in pregnant women. *Cochrane Database Syst Rev*. 2008;(4):CD004912.